

Reward Processing in First - Degree Relatives of Individuals with Schizophrenia

By

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Abstract

Schizophrenia is a psychological disorder that affects individuals' cognitions, behaviors, emotions and ultimately, their ability to function in society. Finding ways to address and treat the abnormalities caused by this disorder could help to better affected individuals' quality of life. This study addresses one such abnormality, dysfunctional reward processing, by studying first-degree relatives of individuals with schizophrenia, since they exhibit similar functional brain differences and are highly vulnerable. I examined whether there were functional connectivity differences between healthy control participants and first-degree relatives of individuals with schizophrenia in three networks: the default mode network (DMN), the salience network (SAL), and the subcortical regions of the reward network (SUB). 30 healthy participants (age range 8-18) and 10 first-degree relatives (age range 8-18) performed a probabilistic learning task while undergoing fMRI. Participants classified abstract stimuli into one of two categories and were given feedback in the form of a monetary reward. Results showed that for SUB within-network functional connectivity, first-degree relatives showed marginally higher mean connectivity than healthy control participants during stimulus presentation. First-degree relatives also showed significantly higher mean connectivity values between brain networks than healthy control participants during stimulus presentation; during feedback, this association was only marginally significant. Results imply that first-degree relatives have more diffuse functional connectivity than healthy controls, which suggests their ability to process information quickly and with targeted intent is less efficient. Future interventions addressing these functional abnormalities could be helpful in treating symptoms of schizophrenia, like anhedonia.

Keywords: Schizophrenia, reward processing, functional connectivity, relatives

Reward Processing in First-Degree Relatives of Individuals with Schizophrenia

Introduction

Schizophrenia is a psychological disorder that affects ~ 1% of the global population and reduces the average potential lifespan of an individual with the disorder by 28.5 years (as cited in Kessler et al., 2005; McGrath, Saha, Chant, & Welham, 2008; Saha, Chant, Welham, & McGrath, 2005; Olfson, Gerhard, Huang, Crystal, & Stroup, 2015). Individuals with schizophrenia face a range of problems related to cognition, behavior, and emotions (Mayo Clinic, 2016). The DSM-V diagnoses individuals with schizophrenia when they display at least one positive symptom – delusions, hallucinations, and/or disorganized speech – and in the absence of a second positive symptom, at least one other symptom such as anhedonia (a negative symptom), gross disorganization, or catatonic behavior (American Psychiatric Association, 2013). Such problems oftentimes affect these individuals' quality of life and ability to function in society. In recent years, researchers have spent time examining one such key problem in individuals with schizophrenia: they experience a sense of anhedonia when it comes to obtaining rewards (Strauss et al., 2014). Such lack of engagement in reward-related behavior suggests abnormal processing of rewards. Reward processing involves our ability to recognize and interpret reward-related stimuli and identify if such reward is gratifying. However, when reward-processing mechanisms are disrupted, as it is in individuals with schizophrenia, it becomes difficult to find satisfaction with daily activities and find motivation to perform tasks, both key aspects that contribute to one's quality of life.

In an effort to better understand this dysfunction, a step necessary to finding and developing better treatment plans for individuals with schizophrenia, numerous researchers have conducted studies examining brain activity levels during both resting and task states, using

patients, first-degree relatives, and healthy control participants as subjects. They used fMRI – a neuroimaging modality that examines a proxy of neural activity, blood oxygen level dependent (BOLD) response. It allows researchers to study the pattern of changes that occur in a particular area of the brain due to variations in regional activity when individuals shift between resting and task states. fMRI studies have shown that schizophrenia patients exhibit diminished fronto-striatal activity when performing cognitive tasks (Zandlbelt et al., 2011; van Veelan et al., 2010; van Veelan et al., 2011). Such findings involving activity have prompted researchers in the past few years to examine whole brain functional connectivity as a way to better understand the mechanisms that give rise to dysfunctional reward processing. Their results showed negative (increased activity in one region associated with decreased activity in another region) connectivity between the midbrain and insula in individuals with schizophrenia, while healthy control participants showed positive connectivity between the same regions (Gradin et al., 2013). Since the midbrain is part of the reward network and the insula is part of the salience network, this suggests dysfunctional between-network connectivity in schizophrenia, a finding that serves as a significant component of this paper's study and hypothesis. However, these previous functional connectivity analyses were conducted using only patients and healthy control participants as subjects (Gradin et al., 2013).

This is important because the brain of a patient with schizophrenia who has taken antipsychotic medication shows differences from that of a patient who has never taken antipsychotic medication; thus, it is not possible to determine whether changes in brain function are due to the illness or to the treatment of the illness (Juckel et al., 2006a; Juckel et al., 2006b). First degree relatives tend to be at higher risk for developing schizophrenia due to their underlying genetic similarity and therefore may display higher levels of cognitive impairments

and changes in brain function related to schizophrenia than people without a familial predisposition to schizophrenia. In support of this, healthy first-degree relatives show similar alterations in task-related brain activity when compared to patients (De Leeuw et al., 2014). By studying the responses of healthy control participants and first-degree relatives of individuals with schizophrenia, researchers can therefore study changes in brain function and cognition that are associated with schizophrenia, without the confounding factor of medication. Consequently, in this current study, I chose to focus on the functional brain connectivity differences between healthy control participants and healthy first-degree relatives of individuals with schizophrenia. This thesis analyzes differences in functional network organization during both stimulus presentation and feedback in a reward processing task. The remainder of this introduction begins by addressing the major role of dopamine in schizophrenia and its relationship to schizophrenia symptomatology and subsequently details newer theories implicating the roles of the default mode network (DMN) and the salience network (SAL) in dysfunctional reward processing.

The Role of the Subcortical Regions in Reward Processing

Researchers have implicated hyperactive dopamine transmission in subcortical areas such as the mesolimbic areas and hypoactive dopamine transmission in the prefrontal cortex as causes for many of the symptoms of schizophrenia (Brisch et al., 2014). Hanssen et al. (2015) suggest that dopamine is also an essential component of motivational learning, reinforcement learning, reward anticipation, and reward prediction error (as cited in Robbins & Everitt, 1996; Schultz, 1997; Bayer & Glimcher, 2005; Juckel et al., 2006b; Drew et al., 2007). It is believed that dopaminergic projections in the mesolimbic system and fronto-striatal network arise in the ventral tegmental region (the midbrain), and then extend to the prefrontal cortex through the dorsal and ventral striatum (Kapur, 2003; Drew et al., 2007). Using fMRI, studies have shown

that schizophrenia patients exhibit abnormal fronto-striatal activity when performing cognitive tasks, which is indicative of functional differences in dopaminergic systems when compared to healthy individuals (Zandlbelt et al., 2011; van Veelan et al., 2010; van Veelan et al., 2011). To better understand this relationship between dopamine and abnormal fronto-striatal activity during reward processing, researchers have found the examination of anhedonia (an inability to feel pleasure) to be of particular importance (Strauss et al., 2014).

There is increasing evidence that individuals with schizophrenia have intact emotional experience, even if they do display signs of anhedonia, an established feature of this disorder (Heerey & Gold, 2007; Bleuler, 1911). Researchers speculate that anhedonia may therefore actually reflect a deficit in anticipatory pleasure or approach motivation rather than a deficit in consummatory pleasure (Burbridge & Barch, 2007; Horan, Green, Kring, & Neuchterlein, 2006; Gard, Kring, Gard, Horan, & Green, 2007). Some suggest that many of the negative symptoms of schizophrenia, including anhedonia, are associated with abnormal ventral striatal reward processing (Gradin et al., 2013). For example, in a study using fMRI to measure brain activity during emotion processing, the right ventral striatum and left putamen showed reduced activation to positive stimuli in individuals with schizophrenia compared to healthy control participants (Dowd & Barch, 2010). Since the ventral striatum is associated with both anticipation and receipt of pleasure from stimuli, the aforementioned reduced right ventral striatal activation may represent a failure to respond to positive experiences, and may contribute to an inability to predict future pleasurable experiences (De Leeuw et al., 2014; Dowd & Barch, 2010). Moreover, correlations between anhedonia and reduced activation in the amygdala and right ventral striatum in individuals with schizophrenia suggest that anhedonia may be the result of failing to mark stimuli as rewarding (Dowd & Barch, 2010). Others also support this theory by reiterating that

this failure to respond to positive factors may contribute to the anticipation and motivation deficits characteristic of symptoms like anhedonia (Berridge & Kringelbach, 2008).

Studies also suggest that such decreases in ventral striatal activity may be due to an increase in dopaminergic tone, something seen in individuals with schizophrenia (Heinz & Schlagenhauf, 2010; Davis, Kahn, Ko, & Davidson, 1991; Howes & Kapur, 2009). According to researchers, abnormal striatal responses may in fact be due to an increased metabolism of dopamine (Corlett et al., 2007; Juckel et al., 2006b; Roiser et al., 2009). Another study has also concluded that dopaminergic dysfunction might potentially be causing the failure of cues signaling potential reward, thereby diminishing ventral striatal activation (De Leeuw et al., 2014). Additionally, correlations between decreased ventral striatal activity during reward anticipation and apathy were also seen in individuals with schizophrenia (Simon et al., 2010). Interestingly, apathy is associated with dysfunctional dopamine activity in the reward network (Bressan & Crippa, 2005). This association reinforces the aforementioned findings by Dowd and Barch (2010) about the relationship between negative symptoms and ventral striatal activity.

De Leeuw et al. (2014) examined reward processing both in the anticipatory and receipt stages in non-affected siblings of schizophrenia patients to further investigate whether such reward-processing deficits are the result of a potential underlying genetic component. Researchers measured the brain activity of unaffected siblings of schizophrenia patients and matched healthy control participants during a modified monetary incentive delay task, which allows the separate investigation of anticipation and receipt of reward. In this task, participants were presented with a reward cue (smiling face) during a rewarding trial or a neutral cue (neutral face) during a non-rewarding trial for 750 milliseconds. Following a brief delay, participants had to press a button to respond as quickly as possible when a target stimulus (exclamation mark)

was presented. If they responded within the allotted time frame, they were given a response of “correct” with an indication of the amount of money they earned.

Regions of interest (ROI) analyses indicated less activity in the ventral striatum, dorsal striatum, right anterior insula and supplementary motor area (SMA) in siblings than in healthy control participants. However, only the difference in activity levels for the left ventral striatum and the left SMA remained significant after researchers corrected for multiple comparisons for the various ROIs (De Leeuw et al., 2014). Comparing siblings and healthy control participants, siblings showed decreased ventral striatal activity during reward anticipation but increased bilateral ventral striatal and orbitofrontal cortex activity during reward receipt (De Leeuw et al., 2014). Such decrease in ventral striatal activity during reward anticipation was also seen in other unaffected first-degree relatives of schizophrenia patients (Grimm et al., 2014). Other researchers have suggested that there may be an association between dysfunction of the prefrontal cortex and abnormal striatal functioning, which is interesting because the prefrontal cortex has connections to the striatum and ventral tegmentum (Guillin, Abi-Dagham, & Laruelle, 2007; Vernaleken et al., 2007; Meyer-Lindenberg et al., 2002).

The above information detailing dysfunctional reward processing with respect to anticipation and receipt in terms of reward network activity and dopaminergic activity give a glimpse into the complicated nature of reward processing in individuals with schizophrenia. The aforementioned research demonstrates that there are a multitude of brain regions and processing factors that are involved and suggest that it is difficult to establish one sole mechanism or factor as being the cause of the reward-processing dysfunctions seen in schizophrenia. Research has subsequently led investigators to examine other brain networks whose functions could

potentially be associated with the abnormal processing of rewards. In this next section, I discuss the role of one of these other networks, the default mode network.

The Role of The Default Mode Network in Reward Processing

The default mode network (DMN) is one of the functional networks whose dysfunctional connectivity with the reward processing network could implicate many of the symptoms associated with deficient reward processing in schizophrenia. Recent research looking into the roles of the DMN in healthy individuals suggests that the network generally shows decreased activation during task-related cognitive processes (Buckner et al., 2008).

In a study analyzing the neural correlates of reward processing in healthy siblings of patients with schizophrenia, Hanssen et al. (2015) gave healthy siblings of schizophrenia patients and healthy control participants a monetary incentive delay task while monitoring their brain activity under fMRI. Whole-brain analyses showed that there were differences between the groups during reward anticipation in that the insula, the posterior cingulate cortex (PCC), and the medial frontal gyrus (MFG) – all areas associated with the DMN – were less deactivated in siblings compared to healthy control participants (Hanssen et al., 2015). Hanssen et al. (2015) suggest that less deactivation in the MFG and PCC during reward processing may indicate a lack of complete disengagement from the DMN; as a result, one isn't able to fully utilize resources for reward-related behavior. Since the DMN is active during internally-focused tasks, less deactivation may indicate an inability to suppress internal thoughts and states, thereby impinging on performance during external, cognitive processes, such as reward anticipation, indicating a

potential endophenotype¹ in the development of schizophrenia symptoms (Hanssen et al., 2015). These results suggest there may be connectivity abnormalities between the DMN and the reward processing network. However, while researchers found hyper-activation of the DMN during reward processing, they also noticed deactivation in the right insula – a region that is part of the salience network (SAL) and involved in cognitive task control (Hanssen et al., 2015). Next, I consider the role of the SAL, whose functions include recruiting different brain regions necessary for processing sensory information (White, Joseph, Francis, & Liddle, 2010).

The Role of the Salience Network in Reward Processing

The insula is a brain region that works in coordination with the anterior cingulate cortex (ACC). Their joint action is detailed as part of the salience network that is thought to allow individuals to switch between the default mode network and task related networks in the service of task goals (Seeley et al., 2007; Taylor et al., 2009; Menon & Uddin, 2010). The importance of this can be seen through Palaniyapan's theory of proximal salience. In this theory, Palaniyapan and Liddle (2011) suggest that an event, such as a sensation or thought, attains "proximal salience" when it gains momentary activity within the SAL, causes an update in expectations, and subsequently initiates or alters an action. Further, this suggests that the SAL is involved in activating brain areas necessary for processing currently relevant stimuli while decreasing the activity in brain regions used to process previously salient stimuli (Palaniyapan & Liddle, 2011).

¹ An endophenotype is defined as a measurable concept that is in-between disease and distal genotype and represents simpler clues to genetic underpinnings than the disease itself (Gottesman & Gould, 2003).

Researchers have examined abnormal functioning in the salience network in an effort to understand reward processing in schizophrenia patients. Previous research citing decreased gray matter and functional abnormalities within the salience network might implicate the salience network in the diminished processing of rewards in schizophrenia patients (Glahn et al., 2008; Wylie & Tregellas, 2010). Additionally, researchers suggest that negative symptoms of the disorder, while linked to the abnormal processing of rewards, may also be tied to patients' incorrect attribution of motivational salience to otherwise neutral/irrelevant stimuli (Kapur, 2003). To investigate this notion and the hypothesis that there may be a disruption of the reward system that accompanies the promotion of false associations, Gradin et al. (2013) examined functional connectivity abnormalities between the salience network and midbrain as a means of studying blunted reward processing in schizophrenia patients. Participants performed a Pavlovian reward task while undergoing fMRI. In each trial, participants were presented with one of two fractal pictures. Two seconds after the picture was presented, participants were rewarded with 0.1 mL of water, or not, according to a random pattern. The pictures were associated with either a high or low probability of water delivery and the picture that was associated with the high probability water delivery changed throughout the task. Participants were told before the start of the trial that the object of the task was to notice which picture was associated most with water delivery and were notified that this association may change throughout the task.

Using the data acquired, researchers conducted a whole brain connectivity analysis by using the dopamine-rich midbrain as a seed region (Gradin et al., 2013). Significant differences in connectivity between the insula and the midbrain were seen between control participants and individuals with schizophrenia, with the latter group showing negative connectivity while the

former group showed positive connectivity (Gradin et al., 2013). Patients also showed decreased connectivity between the midbrain and insula when compared to healthy control participants; this decrease was correlated with increased severity of psychotic symptoms (Gradin et al., 2013). The reduced functional connectivity between the insula and the midbrain indicates reduced integration between the SAL network and the dopaminergic midbrain in schizophrenia patients, which by extension, suggests that the SAL fails to recruit the areas that process reward in patients (Gradin et al., 2013). These points provide additional explanations for the diminished reward processing ability seen in schizophrenia patients that deviates from the traditional dopaminergic theory.

In control participants, connectivity results also showed a significant positive association between increased activity in the midbrain and increased activity in other brain regions (Gradin et al., 2013). Such connections included brain regions within the DMN, like the medial temporal lobe structures, particularly the amygdala-hippocampus complex and the para-hippocampal gyrus (Gradin et al., 2013). Activation was also seen in the bilateral putamen (part of the reward network) and insula (part of the salience network). These positive associations were similar in schizophrenia patients, although less strongly and with limitations in spatial extent (Gradin et al., 2013). Individuals in the control group also exhibited negative functional connectivity between the midbrain and across other brain regions within the SAL (ventral anterior cingulate) and DMN (medial prefrontal cortex and retrosplenial cortex) (Gradin et al., 2013). The pattern was similar but weaker in individuals with schizophrenia. Additionally, patients showed reduced accuracy when compared to control participants in post-scan verbal reports of picture-water associations in the last block of the task (Gradin et al., 2013). This suggests that patients displayed diminished attention and/or impaired learning.

Similar to previous studies, results also showed that patients had reduced ventral striatal responses during reward vs. no reward conditions, which was correlated with the severity of their negative symptoms (Gradin et al., 2013). Their work arose from other researchers' hypothesis, which suggested that reduced reward processing in schizophrenia patients may be linked to negative symptoms often accompanying the disorder (Juckel et al., 2006a; Juckel et al., 2006b). In studying this hypothesis, these researchers examined ventral striatal activation during anticipation of rewards in both medicated and unmedicated patients with schizophrenia and found that both groups exhibited reduced ventral striatal activity (Juckel et al., 2006a; Juckel et al., 2006b). When Gradin et al. (2013) replicated Juckel et al.'s methods, they found that this reduction correlated with the severity of negative symptoms present in the individual, and subsequently concluded that there is an association between negative symptoms and abnormal processing of rewards in the ventral striatum. However, all of these findings may be limited in their generalization due to the small sample size of participants and the fact that the schizophrenia patients were medicated. Nonetheless, the findings regarding abnormal reward processing and the impaired connectivity between the salience and reward network signify a direction for future research.

Current Direction of Research

Researchers have increasingly begun to focus on how the impact of dysfunctional reward processing might be reflected in abnormal functional connectivity patterns. In one particular study, Sharma et al. (2017) conducted a connectome-wide analysis, in which they examined alterations in functional connectivity across all the interregional connections in the brain in individuals with diverse psychopathology. This study was different from previous functional connectivity studies that looked at only a few brain regions. They looked at the relationship

between a dimensional measure of reward responsivity (using the reward sensitivity subscale of the Behavioral Activation Scale) and resting-state functional connectivity. A higher score on the subscale reflected a greater sensitivity to reward. After performing a multivariate distance-based matrix regression, researchers found an association between dimensional deficits in reward responsivity and hyperconnectivity within the DMN (Sharma et al., 2017). They also found an association between impaired reward responsivity and diminished connectivity between the DMN and cingulo-opercular network regions, which overlaps with the SAL (Sharma et al., 2017). Reduced connectivity between the nucleus accumbens and the DMN was also associated with reward deficits, which is interesting since nucleus accumbens abnormalities have previously been linked with anhedonia (Sharma et al., 2017; Wang et al., 2016). These findings once again suggest that symptoms of schizophrenia like anhedonia may be the result of underlying brain network functional connectivity abnormalities.

This introduction explored the role of dopamine in dysfunctional reward processing in schizophrenia, as well as the roles of the DMN and SAL in regulating task-related networks – including the reward processing system. Taken together, these studies suggest a complex pattern of dysfunction with regard to the connectivity between reward processing centers. Further research into the precise nature of this dysfunction can be done with whole brain connectivity analyses, which can identify and quantify inter-regional relationships in the brain, and elucidate researchers about these inter-network influences clearly. In the current study, control participants and individuals were asked to perform a reward-learning task during an fMRI scan. Brain activity was measured during reward anticipation (stimulus presentation) and receipt (feedback). Functional connectivity between brain regions was measured to quantify the statistical association (i.e., correlation) of BOLD responses across time. Methods utilized for this project

were acquired from Cohen et al.'s (2010) study examining adolescent response to prediction errors. On this basis, the current study sought to analyze how alterations in functional connectivity between the DMN and the subcortical regions (SUB) and between the DMN and SAL were different in first-degree relatives of individuals with schizophrenia as compared to healthy control participants. The following functional connectivity hypothesis will ultimately be the focus of this thesis: first-degree relatives of individuals with schizophrenia will show increased within-network functional connectivity for all three networks and decreased between-network functional connectivity when compared to healthy controls during both stimulus presentation and feedback while performing reward-processing tasks.

Method

Participants

67 healthy developing right-handed participants (age range: 8-30) were recruited from the community within a 25-mile radius of the University of California at Los Angeles (UCLA), where this study was conducted. Participants were acquired through online advertisements and random phone calls of available households in the area. Only 61 healthy participants were eligible to participate in the fMRI study. Participants were eligible for the study if they had no history of central nervous system (CNS) disease, DSM-IV disorders, learning disabilities, substance use, or treatment with anti-psychotic drugs in the two years prior. They also could not have any metal in their bodies other than dental fillings and could not be pregnant. 16 adolescent first-degree relatives (age range 8-18) were recruited through previous participation in family studies of child-onset schizophrenia (COS) at UCLA. Only 30 healthy control participants (age range: 8-18) and 10 first-degree relatives (age range: 8-18) of individuals with schizophrenia were ultimately included in the data analysis due to inaccurate, incomplete, or distorted fMRI scans,

demographic information, and/or regions of interest (ROI) data for the other participants. The first-degree relatives were matched in age, education and gender to the healthy control participants.

Procedure

The following procedure is also detailed in the Cohen et al. (2010) paper. In a probabilistic learning task, participants classified abstract stimuli into one of two categories (Northern and Eastern) and were given feedback displaying the correct response at the end of each trial. On each trial, they saw an abstract image representing patterns on a college t-shirt. They were asked to classify the shirt as being worn by someone who attended Northern University (left button press using right index finger) or Eastern University (right button press using right middle finger). The task was probabilistic in that participants were told that individuals other than those who actually attend the university may occasionally wear the shirt; thus, the feedback would not always be consistent for each stimulus (Cohen et al., 2010).

There were two possible stimulus types: predictable (associated 83% of the time with one of the two categories) and random (associated 50% of the time with each category). There were also two possible rewards: large (\$0.25) and small (\$0.05). The stimuli were on the screen for an average of 3,000 ms (ranging between 2,500 and 5,000 ms). During this time, participants had to quickly indicate which university would be associated with the abstract image that was being presented on the screen by pressing the left button with their index finger or the right button with their middle finger. A blank screen served as the interval between trials, with an average duration of 750 ms (ranging between 150 and 1500 ms). There were two, 306-second runs. Each run consisted of 72 trials. At the end of the stimulus presentation, feedback was displayed on the monitor for 1,250 ms. During feedback, participants received information about both the correct

response (which university the stimulus was actually associated with) and the amount of their monetary reward, if they were correct. To ensure motivation, participants were paid the amount of reward they won during the task at the end of the study. The above information is also detailed in Figure 1, which can be found at the end of this paper.

fMRI Data Acquisition

MRI data acquisition parameters are described in detail in the Cohen et al. (2010) paper. As described there, participants performed a probabilistic learning task during fMRI acquisition. They viewed the task through LCD goggles and responded using an MR-compatible button box. Abstract computer-generated stimuli were presented using the ArtMatic Pro, U&I Software LLC. Head movement was minimized using foam padding in an eight-channel head coil. A Siemens Allegra 3T scanner was used to acquire structural and functional scans, such as a high resolution T1-weighted magnetization-prepared, rapid-acquisition gradient echo (MPRage; TR = 2300 ms, TE = 2.1 ms, voxel size = 1.3 x 1.3 x 1 mm, 1 mm isotropic, 160 slice sagittal acquisition, 1 mm slice thickness, matrix 192 x 192 field view of 256). BOLD T2-weighted echoplanar images (EPI) (34 slices, slice thickness = 4 mm, voxel size = 3.1 x 3.1 x 4.00, TR = 2000 ms, TE = 30 ms) were collected for the functional runs during the reward processing task.

fMRI Data Preprocessing

Results included in this manuscript come from preprocessing performed using the latest FMRIprep version, a Nipype based tool (Esteban et al., 2017; Gorgolewski et al., 2011; Gorgolewski et al., 2017). Each T1 weighted volume was skull stripped using antsBrainExtraction.sh v2.1.0 (using OASIS template) (Tustison et al., 2010). Cortical surface was estimated using FreeSurfer v6.0.0 (Dale et al., 1999). The skull-stripped T1 weighted volume was co-registered to skull stripped ICBM 152 Nonlinear Asymmetrical template version

2009c using nonlinear transformation implemented in ANTs v2.1.0 (Fonov et al., 2009; Avants et al., 2008). Functional data was motion corrected using MCFLIRT v5.0.9 (Jenkinson et al., 2002). This was followed by coregistration to the corresponding T1 weighted volume using boundary-based registration at 9 degrees of freedom – implemented in FreeSurfer v6.0.0 (Greve, 2009). Motion correcting transformations, T1 weighted transformation, and MNI template warp were applied in a single step using antsApplyTransformations v2.1.0 with Lanczos interpolation. Three tissue classes were extracted from T1 weighted images using FSL FAST v5.0.9 (Zhang, 2001).

ROI Parcellation

The brain was parcellated into 88 ROIs taken from the Power et al. (2011) functional atlas. These ROIs consisted of the *a priori* defined functional networks, Default Mode Network (DMN), Salience Network (SAL) and Subcortical reward-related regions (SUB)². ROIs were defined as 9x9x9 millimeter voxel cubes centered on the ROI coordinate. See Figure 2 and Table 1.

Functional Connectivity Data Analysis

In neuroscience, functional connectivity is a measure used to quantify correlations in BOLD activity level between different brain regions of interest (ROIs) across time. When the activity levels of two brain regions are significantly correlated (i.e., an increase in activity in one brain region is associated with an increase or decrease in activity in another brain region), this

² Due to the lack of a defined, coherent, reward network, this paper will address the reward network by using subcortical reward-related brain regions. Therefore, this paper will henceforth address the reward related brain regions as the subcortical regions of the reward network (SUB).

indicates that those regions are functionally connected to each other. Functional connectivity can be used to determine relationships between two or more brain regions during both resting and task states. It is important to note that functional connectivity neither provides information about the directional nature of this relationship nor about causality. In this current study, functional connectivity is used to observe the relationships between brain regions as activity level changes over time during a probabilistic learning task.

Beta series correlation. To determine functional connectivity during task states, a beta-series correlation was used. This involves generating parameter estimates – or beta values – using the value of the fMRI BOLD response during a particular trial of interest or phase of a trial. In this study, we were interested in two separable phases within each trial: stimulus presentation and feedback. All trials were included in the beta-series correlation for each phase. Beta series correlation was performed using the Least-Squares Separate method of Mumford, Turner, Ashby and Poldrack (2012), which implements a general linear model that included 32 nuisance regressors (motion parameters, white matter signal and CSF signal, squared terms, lag-1 derivatives, and squared lag-1 derivatives), along with regressors for trial phases of non-interest (i.e., feedback phase for the Stimulus beta-series and stimulus phase for the Feedback beta-series). A highpass filter of .01 mHz was applied to both the design matrix and voxel data. Beta series were calculated across the entire brain independently for Stimulus events and Feedback events. Beta values for each trial phase were temporally sorted, resulting in a beta series containing 144 trials for each phase (Stimulus and Feedback).

Once whole-brain beta-series maps were generated, beta-values were averaged across all voxels within each ROI and correlated across all pairs of ROIs to generate a Pearson's r correlation coefficient between each pair of ROIs. This process was done for regions within the

DMN, SAL, and SUB to create a correlation matrix in which each cell represented the magnitude of the beta-series correlation between ROIs. The correlation coefficients were then standardized to allow for statistics to be conducted. See Figure 3 and Figure 4 for correlation matrices of the networks during stimulus presentation and feedback, respectively.

Functional connectivity metrics. Following ROI parcellation and correlation matrix generation, summary functional connectivity metrics were calculated. Within-network functional connectivity is defined as the average correlation in activity (during a particular trial phase) between brain regions within a functional network. Within-network functional connectivity values were calculated by taking the average beta-series correlation values of ROIs within each network. This measure yielded three within-network connectivity values per trial phase (DMN, SAL, SUB). Between-network functional connectivity is defined as the average correlation in activity (during a particular trial phase) between all functional networks. Between-network functional connectivity values were calculated by taking the average of the average beta-series correlation values of ROIs between two different networks, for all three networks (DMN, SAL, SUB). This measure yielded one between-network connectivity value per trial phase.

Analysis. The independent variable in this study, or the predictor, was the grouping of the individual (first-degree relative of individuals with schizophrenia or healthy control). The dependent variable for fMRI analyses involves the functional connectivity values obtained from the beta series correlation matrix constructed using the fMRI BOLD response level measured over time. Using the previously described functional connectivity metrics as our target outcomes, we examined the relation of these outcomes to first degree relative status. Independent samples t-tests were used to compare differences in mean functional connectivity values between first-

degree relatives and healthy control participants during both trial phases within and between networks. All statistical tests were performed using SPSS version 24.

Results

Mean Differences During Stimulus Presentation

Independent samples *t*-tests of average functional within and between network connectivity values were performed to understand whether there were differences between healthy control participants and first-degree relatives with regards to how functionally connected various brain regions within and between each network are. The descriptive statistics that are presented in this section are detailed in Table 2. Differences in mean functional connectivity values between healthy control participants and first-degree relatives during stimulus presentation are detailed in Figure 5. The significance level was set at $\alpha = 0.05$.

DMN within-network connectivity. During stimulus presentation, there were no significant mean functional connectivity differences between first-degree relatives and healthy control participants within the DMN: $t(38) = -1.447, p = 0.156$.

SAL within-network connectivity. There were no significant mean functional connectivity differences between first-degree relatives and healthy control participants within the salience network during stimulus presentation either: $t(10.991) = -1.324, p = 0.212$. The aforementioned degrees of freedom are less than 38 because the Levene's Test for Equality of Variances was significant, suggesting that equality of variances cannot be assumed for this data value.

SUB within-network connectivity. During stimulus presentation, there were marginally significant mean differences in functional connectivity between relatives and healthy control participants within the subcortical regions: $t(38) = -1.985, p = 0.054$. First-degree relatives

showed higher mean connectivity values ($M = 0.314$, $SD = 0.112$) than healthy control participants ($M = 0.245$, $SD = 0.090$).

Between-network connectivity. Additionally, during stimulus presentation, first-degree relatives showed significant mean differences from healthy control participants with regards to overall connectivity between networks: $t(38) = -2.148$, $p = 0.038$. First-degree relatives showed higher mean connectivity values between the brain networks ($M = 0.177$, $SD = 0.089$) than healthy control participants ($M = 0.121$, $SD = 0.066$).

Mean Differences During Feedback

Independent samples t -tests of average functional within and between network connectivity values were once again performed during feedback. This was done to understand whether there were differences between healthy control participants and first-degree relatives with regards to how functionally connected various networks are when receiving feedback. The descriptive statistics that are presented in this section are detailed in Table 3. Differences in mean functional connectivity values between healthy control participants and first-degree relatives during feedback are detailed in Figure 6. The significance level was set at $\alpha = 0.05$.

DMN within-network connectivity. During feedback, there were no significant mean functional connectivity differences between first-degree relatives and healthy control participants within the DMN: $t(10.854) = -1.116$, $p = 0.289$.

SAL within-network connectivity. There were no significant mean functional connectivity differences between first-degree relatives and healthy control participants within the salience network either during feedback: $t(38) = -1.077$, $p = 0.288$.

SUB within-network connectivity. During feedback, there were no significant mean differences in functional connectivity between relatives and healthy control participants within the subcortical regions: $t(38) = -1.641, p = 0.109$.

Between-network connectivity. During feedback, first-degree relatives showed marginally significant mean differences from healthy control participants with regards to overall connectivity between networks: $t(38) = -1.807, p = 0.079$. First-degree relatives showed higher mean connectivity values ($M = 0.169, SD = 0.090$) than healthy control participants ($M = 0.121, SD = 0.066$).

Discussion

The goal of this investigation was to determine the extent to which within and between network functional connectivity was different between first degree relatives of patients with schizophrenia and healthy control participants during a reward learning task. We hypothesized that first-degree relatives would show increased within-network connectivity for the DMN, SAL, and SUB and decreased connectivity between networks. Results showed marginally increased within-network connectivity for the SUB during stimulus presentation but not for any of the other networks during both stimulus presentation and feedback, although numerically results for all networks were consistent with our hypothesis. Results also showed significantly increased connectivity between networks during both stimulus presentation and feedback, which was the opposite relationship of what was originally predicted.

The increased within-network connectivity for the SUB during stimulus presentation is inconsistent with prior literature that showed decreased functional connectivity between the midbrain and bilateral putamen in schizophrenia patients compared to healthy controls (Gradin et al., 2013). However, there has been minimal prior investigation regarding the within-network

connectivity of the reward network. Furthermore, this discrepancy in findings may partially be due to the fact that the individuals in the current study were first-degree relatives whereas the participants in the previous study were medicated patients. Further investigation can help understand if these functional connectivity differences are associated with individuals' progression from an at-risk state to clinical diagnosis. Nonetheless, this increased within-network functional connectivity in the SUB during reward processing may suggest that first-degree relatives face difficulty in responding to rewarding stimuli due to the hyperconnectivity of reward-processing regions. This notion is supported by prior research that suggested that symptoms of schizophrenia like anhedonia may reflect an inability to mark salient stimuli as rewarding (Dowd & Barch, 2010). Furthermore, prior research has also suggested that apathy, another negative symptom, is associated with dysfunctional dopamine activity in the reward network (Bressan & Crippa, 2005). Therefore, this abnormal functional connectivity in the subcortical regions of the reward network may partially be explained by dysfunctional dopamine activity. These two factors in combination may explain the overall level of dysfunctional reward processing in relatives of patients with schizophrenia.

Additionally, the increased between-network connectivity during both stimulus presentation and (marginally) during feedback implies that first-degree relatives have more dispersed functional connectivity than healthy controls during tasks, which suggests their ability to process information quickly and with targeted intent is less efficient. During stimulus presentation, the hyperconnectivity between brain areas might potentially be diminishing first-degree relatives' ability to respond to newly salient, potentially rewarding, stimuli. This idea is supported by prior research which suggests negative symptoms like anhedonia may be tied to patients' incorrect attribution of motivational salience to otherwise neutral/irrelevant stimuli

(Kapur, 2003). However, the overall notion that there is increased between-network connectivity is inconsistent with prior research which suggested that decreased connectivity between the insula (a region associated with the SAL) and the midbrain (a region associated with the SUB) should reflect reduced integration and failure of the SAL to recruit areas that process rewards in patients (Gradin et al., 2013). In additional support of this inconsistency, other researchers have also suggested that reduced connectivity between the DMN and nucleus accumbens reflects reduced integration of brain networks involved in reward processing (Sharma et al., 2017). This discrepancy may be present partially because the current study examined between-network functional connectivity during a task state in first-degree relatives whereas the previous research by Gradin et al. (2013) studied medicated patients and that by Sharma et al. (2017) studied resting-state related connectivity in medicated patients. Another reason for this discrepancy may be the limited sample size of the first-degree relative participant pool, which could have yielded a lack of sufficient data necessary to analyze the relative increased or decreased connectivity when compared to healthy controls.

Although there was a lack of significant differences in within-DMN functional connectivity, the results of this study were still numerically consistent with prior literature suggesting hyperconnectivity of the DMN during resting state in individuals with heterogeneous psychopathology (Sharma et al., 2017). Since numerically there was greater within-DMN connectivity, a larger sample size may be needed to have the power to study this association.

Through this research, we were able to analyze the underlying functional connectivity mechanisms by which abnormal reward processing may potentially be occurring in individuals with schizophrenia. The results of the study demonstrate that functional abnormalities associated with the disorder are due to not just one particular brain region but are the result of

interconnected relationships between multiple brain networks and regions. Unlike previous research which has primarily focused on activation of these brain regions during reward processing, this study has examined underlying functional network connectivity abnormalities during task states in first-degree relatives of individuals with schizophrenia. However, the low sample size of first-degree relatives, when compared to the corresponding group of healthy control participants utilized in this study, is a major limitation in making definitive conclusions about functional connectivity abnormalities' impact on reward processing.

However, the interesting findings in the study present a direction for future research. The first step in further studying the topics presented in this paper include defining a reward network that encompasses all of the brain regions associated with processing reward. In this study, only the subcortical regions of the reward network were utilized. Examining functional connectivity across the reward network using all of the ROIs associated with it would yield more holistic results with regards to within and between network connectivity. Secondly, a larger sample size of first-degree relatives and healthy control participants ranging in age from childhood to adolescence to adulthood could give a better indication of how functional reward processing abnormalities develop and change over time. A lack of analysis of behavioral data is also a limitation. An examination of group differences in accuracy and response time will help to better understand the relationships between behavior, schizophrenia symptomology, and reward processing deficits. Another step for studying dysfunctional reward processing could involve identifying associations between structural brain development abnormalities and the functional connectivity abnormalities that have thus far been identified. This direction of research could help bridge information regarding neurobiological and neuropsychological abnormalities that

underlie the symptoms related to schizophrenia and other psychological disorders so that researchers and clinicians can find ways to help improve affected individuals' quality of life.

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Footnotes

¹ An endophenotype is defined as a measurable concept that is in-between disease and distal genotype and represents simpler clues to genetic underpinnings than the disease itself (Gottesman & Gould, 2003).

² Due to the lack of a defined, coherent, reward network, this paper will address the reward network by using subcortical reward-related brain regions. Therefore, this paper will henceforth address the reward related brain regions as the subcortical regions of the reward network (SUB).

Table 1.

Brain Regions of Interest (ROIs) Within Each Network

Power ROI ID	X	Y	Z	System	Closest AAL Region
74	-40.5	-75.27	25.8	Default mode	Occipital_Mid_L
75	5.55	66.69	-3.55	Default mode	Frontal_Med_Orb_R
76	8.36	47.59	-15.18	Default mode	Rectus_R
77	-12.6	-39.64	0.93	Default mode	Lingual_L
78	-17.65	63.19	-9.17	Default mode	Frontal_Sup_Orb_L
79	-45.79	-60.69	20.85	Default mode	Temporal_Mid_L
80	43.43	-72.21	28	Default mode	Occipital_Mid_R
81	-43.58	11.99	-34.15	Default mode	Temporal_Pole_Mid_L
82	45.64	16.2	-30.02	Default mode	Temporal_Pole_Mid_R
83	-68.47	-22.66	-15.74	Default mode	Temporal_Inf_L
86	-44.45	-64.64	34.78	Default mode	Angular_L
87	-39.05	-74.95	43.72	Default mode	Parietal_Inf_L
88	-6.84	-54.9	27.05	Default mode	Precuneus_L
89	5.91	-58.82	35.45	Default mode	Precuneus_R
90	-11.29	-56.2	15.6	Default mode	Precuneus_L
91	-2.94	-48.79	12.87	Default mode	Precuneus_L
92	7.94	-48.37	30.57	Default mode	Cingulum_Post_R
93	15.12	-63.09	25.98	Default mode	Precuneus_R
94	-2.2	-36.68	43.85	Default mode	Cingulum_Mid_L
95	10.77	-53.83	17.09	Default mode	Precuneus_R
96	52.04	-59.37	35.52	Default mode	Angular_R
97	23.33	33.07	47.68	Default mode	Frontal_Sup_R
98	-10.09	39.09	52.29	Default mode	Frontal_Sup_Medial_L
99	-16.4	28.52	53.05	Default mode	Frontal_Sup_L
100	-35.36	19.86	50.8	Default mode	Frontal_Mid_L
101	22.11	39.21	38.9	Default mode	Frontal_Sup_R
102	12.73	54.87	38.19	Default mode	Frontal_Sup_R
103	-10.33	54.63	38.71	Default mode	Frontal_Sup_L
104	-19.78	45.07	39.48	Default mode	Frontal_Sup_L
105	5.94	54.42	16.18	Default mode	Frontal_Sup_Medial_R
106	6.11	63.98	21.96	Default mode	Frontal_Sup_Medial_R
107	-7.04	50.82	-1.29	Default mode	Cingulum_Ant_L
108	8.8	54.23	3.45	Default mode	Frontal_Sup_Medial_R
109	-3.06	44.41	-9.46	Default mode	Frontal_Med_Orb_L
110	7.51	42.49	-5.35	Default mode	Frontal_Med_Orb_R
111	-11.06	44.62	7.61	Default mode	Cingulum_Ant_L
112	-2.06	37.85	36.34	Default mode	Frontal_Sup_Medial_L
113	-2.5	41.7	16.05	Default mode	Cingulum_Ant_L
114	-20.16	63.65	19.39	Default mode	Frontal_Sup_L
115	-7.55	48.08	23.18	Default mode	Frontal_Sup_Medial_L
116	64.64	-11.8	-19.3	Default mode	Temporal_Mid_R

117	-55.72	-12.96	-10.24	Default mode	Temporal_Mid_L
118	-57.75	-29.7	-3.94	Default mode	Temporal_Mid_L
119	64.8	-30.55	-8.7	Default mode	Temporal_Mid_R
120	-68.3	-41.41	-5.14	Default mode	Temporal_Mid_L
121	13.08	29.99	58.65	Default mode	Frontal_Sup_R
122	12.25	35.63	20.3	Default mode	Cingulum_Ant_R
123	52.16	-2.43	-16.4	Default mode	Temporal_Mid_R
124	-26.44	-39.95	-8.26	Default mode	ParaHippocampal_L
125	26.94	-37.34	-12.76	Default mode	Fusiform_R
126	-33.93	-38.06	-15.6	Default mode	Fusiform_L
128	51.9	6.81	-29.61	Default mode	Temporal_Pole_Mid_R
129	-52.89	2.55	-27.06	Default mode	Temporal_Mid_L
130	46.68	-50.08	28.76	Default mode	Angular_R
131	-49.3	-42.15	0.83	Default mode	Temporal_Mid_L
137	-46.17	31.26	-13.03	Default mode	Frontal_Inf_Orb_L
139	49.26	35.47	-12.2	Default mode	Frontal_Inf_Orb_R
203	10.51	-38.54	50.02	Salience	Cingulum_Mid_R
204	55.27	-44.59	36.7	Salience	SupraMarginal_R
205	42.05	-0.39	47.1	Salience	Precentral_R
206	31.24	32.79	26.39	Salience	Frontal_Mid_R
207	47.6	22.16	9.74	Salience	Frontal_Inf_Tri_R
208	-35.44	20.03	0.07	Salience	Insula_L
209	35.91	21.91	2.62	Salience	Insula_R
210	36.89	32.35	-2.24	Salience	Frontal_Inf_Orb_R
211	33.56	16.45	-7.58	Salience	Insula_R
212	-10.76	25.99	24.54	Salience	Cingulum_Ant_L
213	-0.94	14.86	43.99	Salience	Cingulum_Mid_L
214	-27.5	52.04	21.28	Salience	Frontal_Mid_L
215	-0.2	30.35	27.22	Salience	Cingulum_Ant_L
216	5.23	23.22	37.03	Salience	Cingulum_Mid_R
217	10.26	22.06	27.48	Salience	Cingulum_Ant_R
218	31.07	55.71	14.49	Salience	Frontal_Sup_R
219	26.07	49.56	26.58	Salience	Frontal_Mid_R
220	-39.12	50.79	17.38	Salience	Frontal_Mid_L
222	6.3	-23.68	-0.42	Subcortical	Thalamus_R
223	-1.77	-13.05	11.82	Subcortical	Thalamus_L
224	-10.28	-18.48	7.04	Subcortical	Thalamus_L
225	11.75	-17.18	7.54	Subcortical	Thalamus_R
226	-5.33	-28.08	-4.13	Subcortical	Thalamus_L
227	-21.97	7.48	-4.78	Subcortical	Putamen_L
228	-15.41	3.57	7.99	Subcortical	Pallidum_L
229	30.5	-13.92	1.65	Subcortical	Putamen_R
230	23.26	10.19	1.46	Subcortical	Putamen_R
231	28.52	0.82	4.01	Subcortical	Putamen_R
232	-31.38	-11.48	-0.3	Subcortical	Putamen_L
233	14.98	4.94	7.24	Subcortical	Pallidum_R

234	8.62	-3.57	5.76	Subcortical	Thalamus_R
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Note. The above table presents the MNI coordinates of each ROI in the brain. It also details the network (SUB, DMN, or SAL) within which each of the regions is found and has been classified for analysis in this study.

Table 2.

Mean and Standard Deviations for Functional Network Connectivity Values During Stimulus Presentation

	DMN Within-Network Connectivity	Salience Within-Network Connectivity	<i>Subcortical</i> <i>Within-Network</i> <i>Connectivity</i>	Between- Network Connectivity
Healthy Controls	0.185 (0.059)	0.198 (0.066)	0.245 (0.090)	0.121 (0.066)
First-Degree Relatives	0.220 (0.087)	0.250 (0.117)	0.314 (0.112)	0.177 (0.089)

Note. The above table presents the mean and standard deviations (in parentheses) for outcomes for healthy controls and first-degree relatives of individuals with schizophrenia. Bolded outcome variables indicate significance at the level $\alpha = 0.05$. Italicized values indicate trending or marginal significance.

Table 3.

Mean and Standard Deviations for Functional Network Connectivity Values During Feedback

	DMN Within-Network Connectivity	Salience Within-Network Connectivity	Subcortical Within-Network Connectivity	<i>Between Network Connectivity</i>
Healthy Controls	0.182 (0.051)	0.203 (0.073)	0.246 (0.094)	0.121 (0.066)
First-Degree Relatives	0.217 (0.094)	0.233 (0.091)	0.304 (0.103)	0.169 (0.090)

Note. The above table presents the mean and standard deviations (in parentheses) for outcomes for healthy controls and first-degree relatives of individuals with schizophrenia. Bolded outcome variables indicate significance at the level $\alpha = 0.05$. Italicized variables indicate trending or marginal significance.

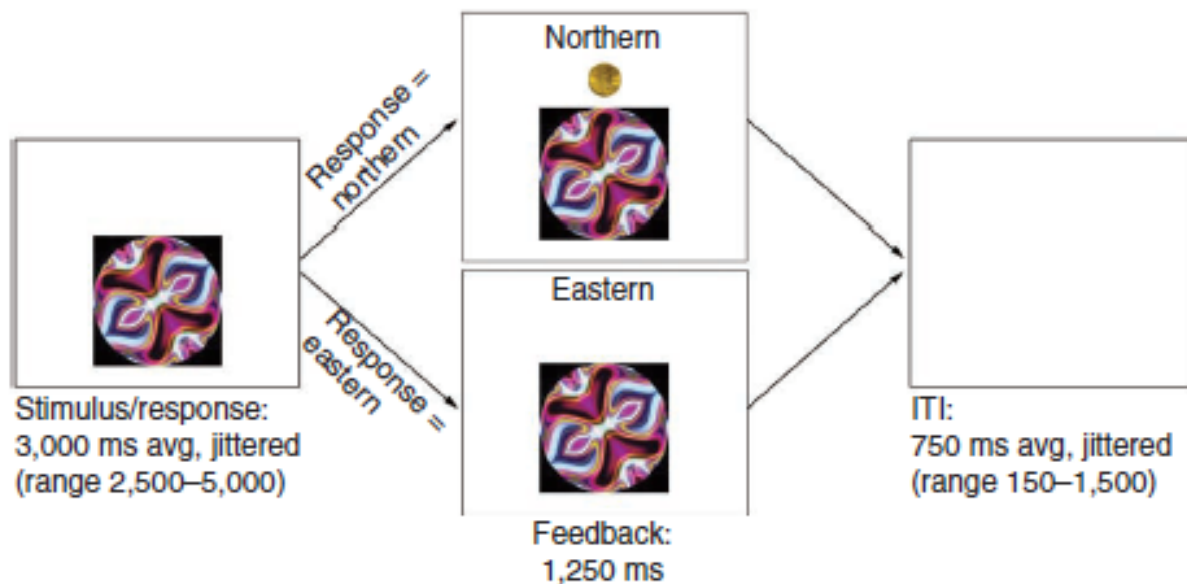


Figure 1. Experimental design acquired from the Cohen et al. (2010) paper. 30 healthy control participants and 10 first-degree relatives of individuals with schizophrenia, both groups aged 8–18 years, performed a probabilistic learning task during fMRI scan acquisition. Participants classified abstract stimuli into one of two categories. If their response accurately matched the outcome, they were given feedback in terms of a monetary reward, displayed as a coin on the screen. There were two stimulus types, predictable (associated 83% of the time with one of the two categories) and random (associated 50% of the time with each category). There were also two reward types, large (\$0.25) and small (\$0.05).

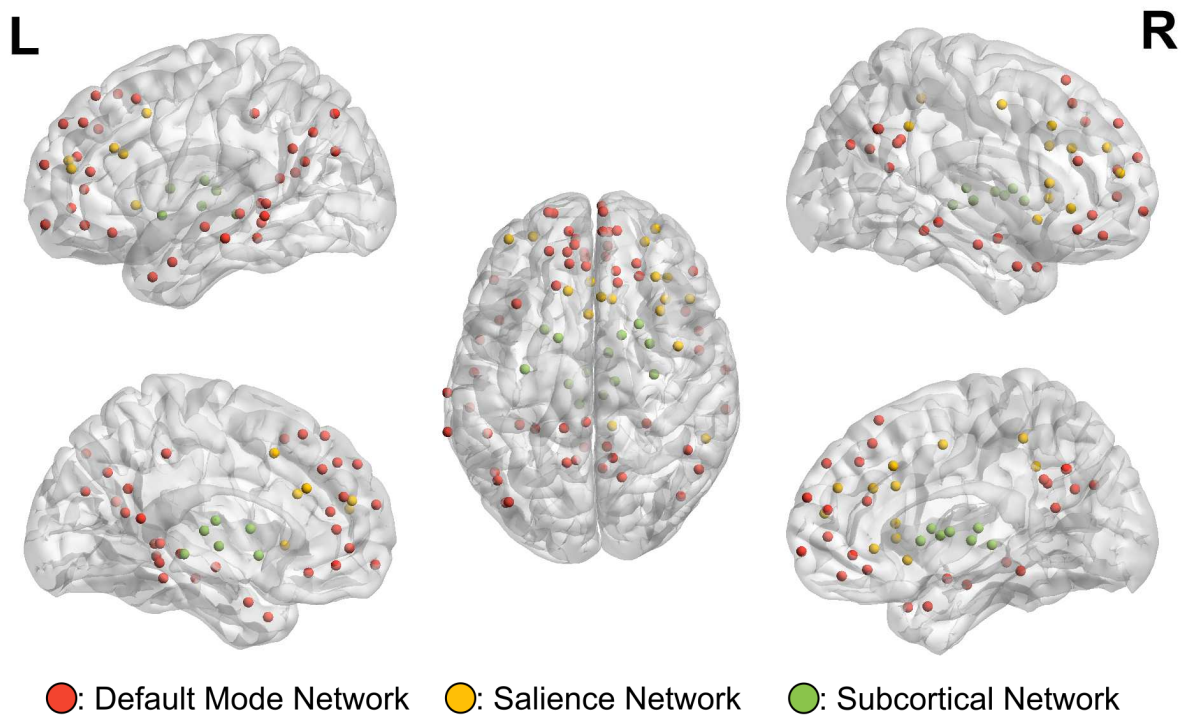


Figure 2. Regions of Interest (ROIs) across the brain for the default mode network, salience network, and subcortical reward related regions.



Figure 3. Correlation matrices computed using beta-series correlation values during stimulus presentation for ROIs within the default mode network, the salience network, and the subcortical reward related regions. First-degree relatives appear to have higher overall between-network connectivity during stimulus presentation.

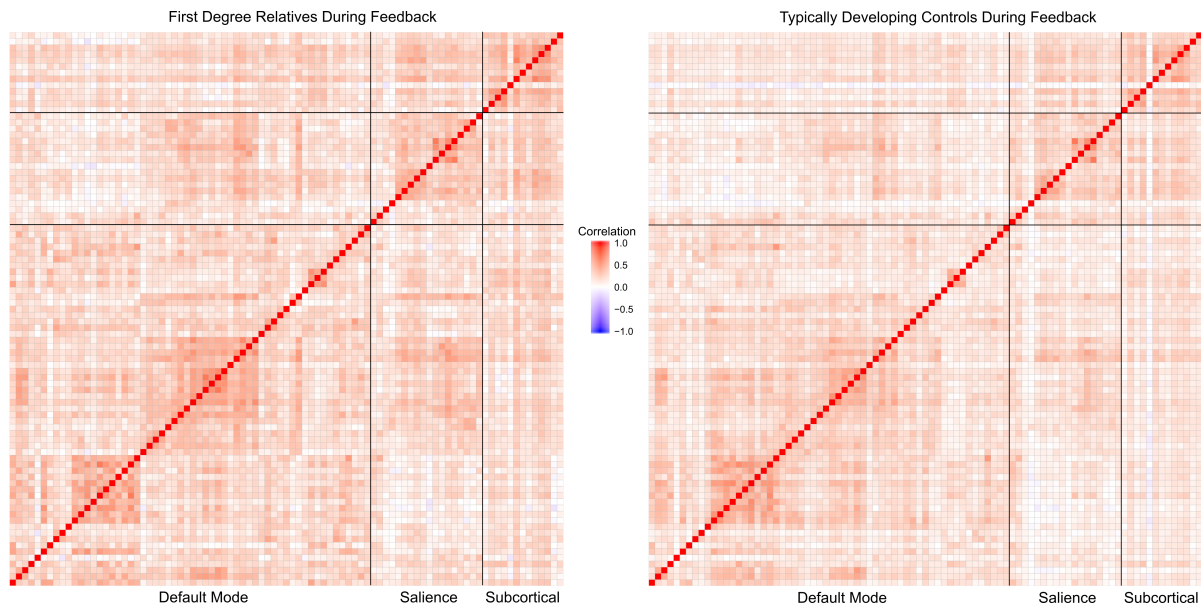


Figure 4. Correlation matrices computed using beta-series correlation values during feedback for ROIs within the default mode network, the salience network, and the subcortical reward related regions. First-degree relatives appear to have higher overall between-network connectivity during feedback.

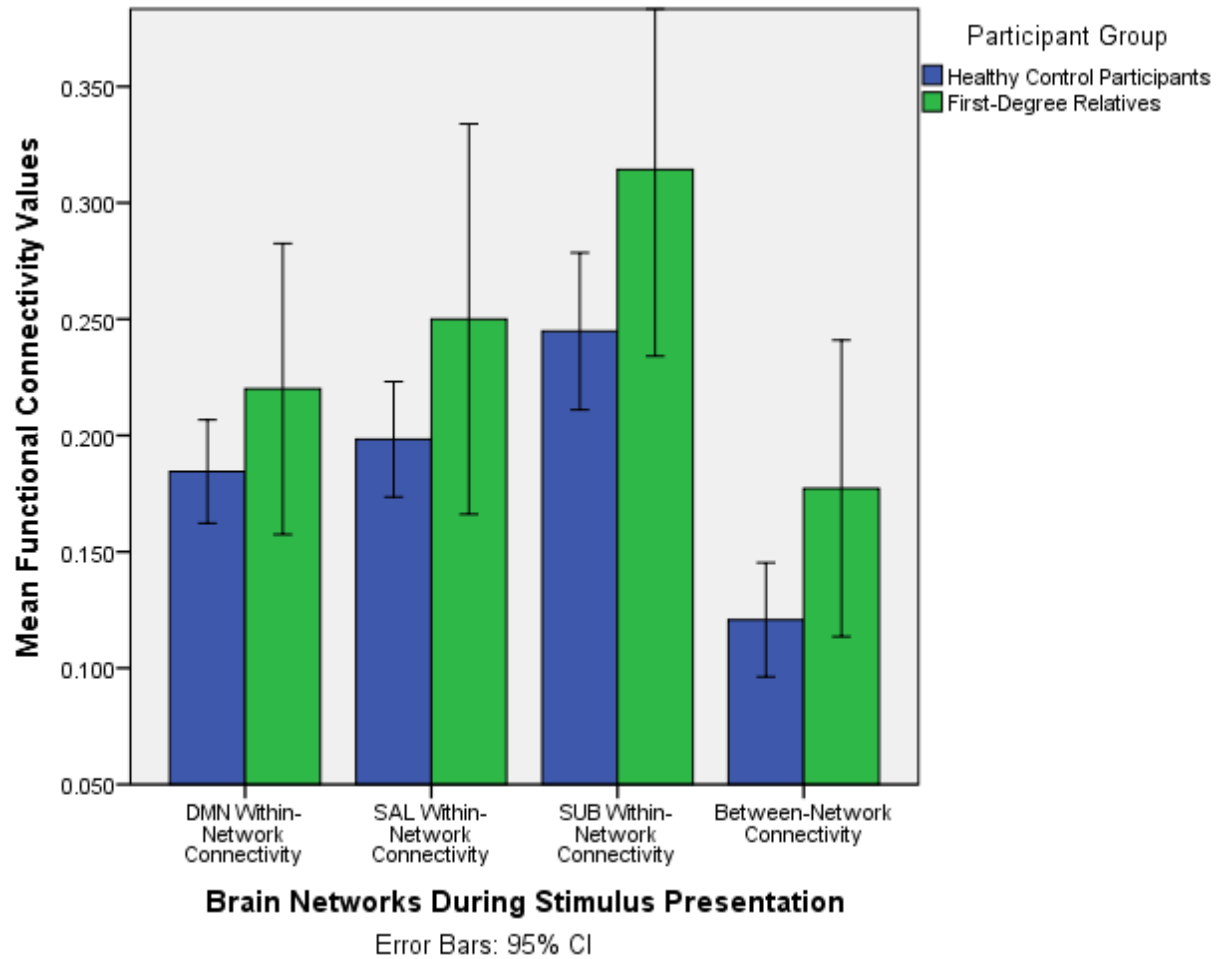


Figure 5. Mean within and between network functional connectivity values for the default mode network, salience network, and subcortical reward related brain regions during stimulus presentation. SUB within-network connectivity differences are marginally significant and between-network connectivity differences are significant on the above graph.

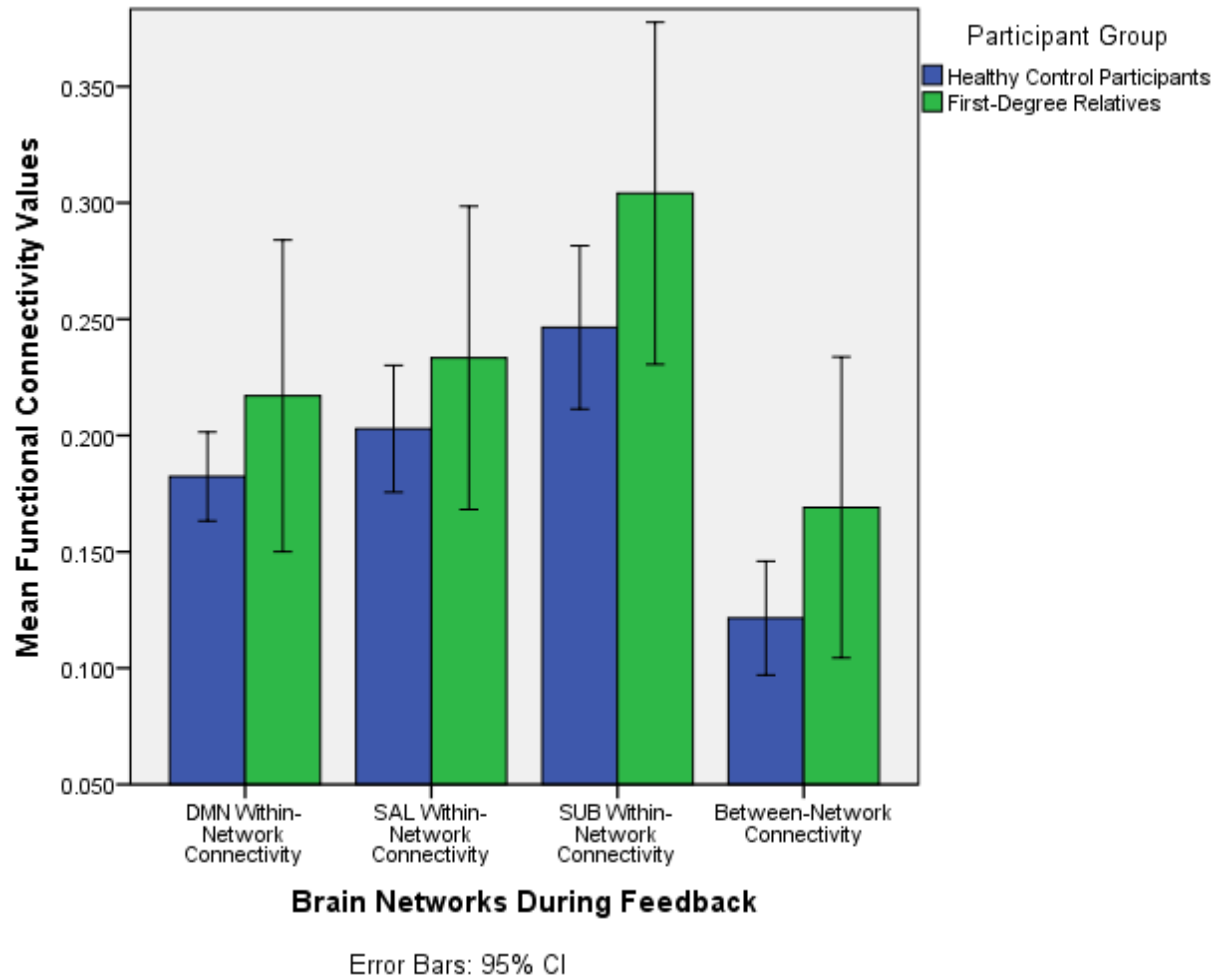


Figure 6. Mean within and between network functional connectivity values for the default mode network, salience network, and subcortical reward related brain regions during feedback. Between-network connectivity differences on the above graph are marginally significant.